

Exhibit A:
Copy of Lab Notebook LB137
pages 1-13

AIM- Formulation calculations for Budesonide concentrated suspensions of differing Budesonide and Polysorbate 80 content.

~~The concentrated suspensions are to be manufactured according to Development Protocol D, M.P. [REDACTED]~~

The Formulation of Budesonide Inhalation Suspension is given in Report R117.

Budesonide Ph. Eur	0.5mg/mL
Polysorbate 80 Ph. Eur	0.2mg/mL
Sodium Chloride Ph. Eur	8.5mg/mL
Sodium Citrate Dihydrate Ph. Eur	0.5mg/mL
Citric Acid Monohydrate Ph. Eur	0.28mg/mL
Disodium Edetate Dihydrate Ph. Eur	0.1mg/mL
Water for Injections	2mL Fill volume

Concentrated Budesonide Suspension (A)

- needs to have a Budesonide concentration of 37.5 mg/mL
- needs to have a Polysorbate 80 content of 5% of the total which will be present upon dilution with placebo to form the final product suspension (as detailed in R117).
- all other excipients should be the same concentration as in the final product suspension (as stated in R117)

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To make up the final product suspension from (A), would have to dilute by a factor of:

$$\frac{37.5}{0.5} = 75 \quad \begin{array}{l} \text{(Budesonide conc in A)} \\ \text{(Budesonide conc in final product suspension)} \end{array}$$

$$\begin{array}{l} \text{Polysorbate 80} \\ \text{content of (A)} \end{array} = \begin{array}{l} \text{Polysorbate 80} \\ \text{content of final} \\ \text{product} \end{array} \times \begin{array}{l} \text{Dilution} \\ \text{factor} \end{array} \times \frac{5}{100}$$

(the 5/100 is due to needing 5% of Polysorbate 80 content of final product suspension in (A))

$$\begin{aligned} \text{Therefore, Polysorbate 80 content of (A)} &= 0.2 \times 75 \times \frac{5}{100} \\ &= \underline{0.75 \text{ mg/mL}} \end{aligned}$$

Concentrated Budesonide Suspension (B)

- the same as (A) but with a Budesonide concentration of 75 mg/mL

Dilution factor to make up final product suspension from (B)

$$= \frac{75}{0.5} = 150$$

$$\begin{aligned} \text{Polysorbate 80 content of (B)} &= 0.2 \times 150 \times \frac{5}{100} \\ &= \underline{1.50 \text{ mg/mL}} \end{aligned}$$

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Concentrated Budesonide Suspension ©

- needs to have a Budesonide concentration of 75 mg/mL
- needs to have a Polysorbate 80 content of 100% of the total which will be present upon dilution with placebo to form the final product suspension (with formulation as stated in R117)
- all other excipients should be the same concentration as in the final product suspension

Dilution factor to make up the final product suspension from ©

$$= \frac{75}{0.5} = 150$$

Therefore, the Polysorbate 80 content of © = $0.2 \times 150 \times 10$
 $= 30 \text{ mg/mL}$

Concentrated Budesonide Suspension ①

- the same as © but with a Budesonide concentration of 150 mg/mL

Dilution factor to make up the final product suspension from ①

$$= \frac{150}{0.5} = 300$$

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Therefore, the Polysorbate 80 content of ① = $0.2 \times 300 \times 100$
 $= 60 \text{ mg/mL}$

Based on the calculations above, the formulations of the concentrated Budesonide suspensions ①, ③, ④ and ⑤ are as stated in Table 1 below.

Table 1 - Formulations of Concentrated Budesonide Suspensions.

	Concentration (mg/mL)	
Budesonide	A	37.5
	B	75
	C	75
	D	150
Polysorbate 80 Ph. Eur	A	0.75
	B	1.50
	C	30
	D	60
Sodium Chloride Ph. Eur	A, B, C, D	8.5
Sodium Citrate Dihydrate Ph. Eur	A, B, C, D	0.5
Citric Acid Monohydrate Ph. Eur	A, B, C, D	0.28
Disodium Edetate Dihydrate Ph. Eur	A, B, C, D	0.1
Water for Injections	A, B, C, D	to 1 mL

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Formulation of placebo required to dilute (A) to form a final product suspension with the formulation stated in R117

Polyorbate 80 concentration in (A) = 0.75 mg/mL

Polyorbate 80 concentration in final product suspension = 0.20 mg/mL

Polyorbate 80 concentration in placebo required for dilution = x mg/mL

→ From LB137 p2, dilution factor = 75

→ Polyorbate 80 = Polyorbate 80 + Polyorbate 80
 (1) content of final product suspension contents of (A) content of placebo

→ Content = concentration × volume

Therefore, using equation (1)

$$(75 \times 0.2) = (1 \times 0.75) + (74 \times x)$$

$$x = \frac{(75 \times 0.2) - (1 \times 0.75)}{74}$$

$$= 0.1926 \text{ mg/mL}$$

Formulation of placebo required to dilute (B) to form a final product suspension with the formulation stated in R117

Polyorbate 80 concentration in (B) = 1.50 mg/mL

From LB137 p2, dilution factor = 150

Therefore, using equation ①

$$\begin{aligned} \text{Polysorbate 80} &= \frac{(150 \times 0.2) - (1 \times 1.5)}{149} \\ \text{concentration in} & \\ \text{placebo needed} & \\ \text{to dilute ③} & \\ &= \underline{0.1913 \text{ mg/mL}} \end{aligned}$$

For ③ and ④, 100% of the Polysorbate 80 present in the final product suspension upon dilution is present in ③ and ④. Therefore, no Polysorbate 80 is present in the placebo used for dilution.

The formulations of the placebo batches required to dilute ②, ③, ④ and ⑤ to form product suspensions as stated in R117 are detailed in Table 2 below.

Table 2.

	Concentration (mg/mL)	
Polysorbate 80 Ph. Eur	A	0.1926
	B	0.1913
	C	0
	D	0
Sodium Chloride Ph. Eur	A, B, C, D	8.5
Sodium Citrate Dihydrate Ph. Eur	A, B, C, D	0.5
Citric Acid Monohydrate Ph. Eur	A, B, C, D	0.28
Disodium Edetate Dihydrate Ph. Eur	A, B, C, D	0.1
Water for Injections	A, B, C, D	to mL

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Aim: To manufacture 4 concentrates with varying concentrations of Polysorbate 80 and Budesonide, for autoclaving and then assaying for chemical degradation.

	BUDESONIDE	POLYSORBATE 80
• Conc. A	37.5mg/ml 18.75g for 500ml batch	0.75mg/ml 0.375g in 500ml
• Conc. B	75mg/ml 37.5g for 500ml batch	1.5mg/ml 0.75g in 500ml
• Conc. C	75mg/ml 37.5g for 500ml batch	30mg/ml 15g in 500ml
• Conc. D	150mg/ml 75g for 500ml batch	60mg/ml 30g in 500ml

Equipment: • Balance - Sartorius AC2105 110 NR: 0068661
• Magnetic Stirrer
• Silverson LR4 Mixer

SAMPLES: Budesonide Placebo without Polysorbate 80.
Batch: LB087 P185

METHOD:

1. In a 600ml beaker, weigh out the correct amount of Polysorbate
2. Add 500ml of Placebo ex: LB087 P185
3. Mix using a magnetic stirrer for 10 minutes.
4. Portion 100-200ml of the mixture into another beaker for the final flush of the Silverson head.
5. Place under the Silverson mixer the remaining solution and add Budesonide slowly until the Budesonide has completely been homogenised.
6. Homogenise for 10 minutes after all the Budesonide has been added.
7. Flush the Silverson head with the remaining Placebo mixture (keeping back ~50ml)

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8. Mix under the magnetic stirrer for 15 minutes to allow for all the foam to disappear.
9. Add the concentrate to a 500ml volumetric flask and make to volume with the remaining some of placebo.
10. Remove any air bubbles that have foamed on the top of the suspension by blowing it with air.

LB137 P9

10:04:07

N 0.0000 g

N + 0.3763 g

CONCENTRATE A

TWEEN 80 BN: 4001

N 0.0000 g

N + 0.7518 g

CONCENTRATE B

TWEEN 80 BN: 4001

N + 0.0000 g

N + 15.0045 g

CONCENTRATE C

TWEEN 80 BN: 4001

N - 0.0001 g

N - 0.0001 g

N 0.0000 g

N + 30.0023 g

CONCENTRATE D

TWEEN 80 BN: 4001

N 0.0000 g

N + 18.8450 g

N + 0.0115 g

CONCENTRATE A
SOL DE MEXICO BINDER

BN: 5268N03A-0m

N 0.0000 g

N + 37.5972 g

N + 0.0261 g

CONCENTRATE B
BINDER

N 0.0000 g

N + 37.5641 g

N + 0.0150 g

CONCENTRATE C
BINDER

N 0.0000 g

N + 75.0978 g

N + 0.0172 g

CONCENTRATE D
BINDERWeights for Tween 80 and
Binder for the Concentrates
A, B, C and D.BINDER
Conc A. = 18.8335 g

Conc B. = 37.5711 g

Conc C. = 37.5491 g

Conc D. = 75.0806 g

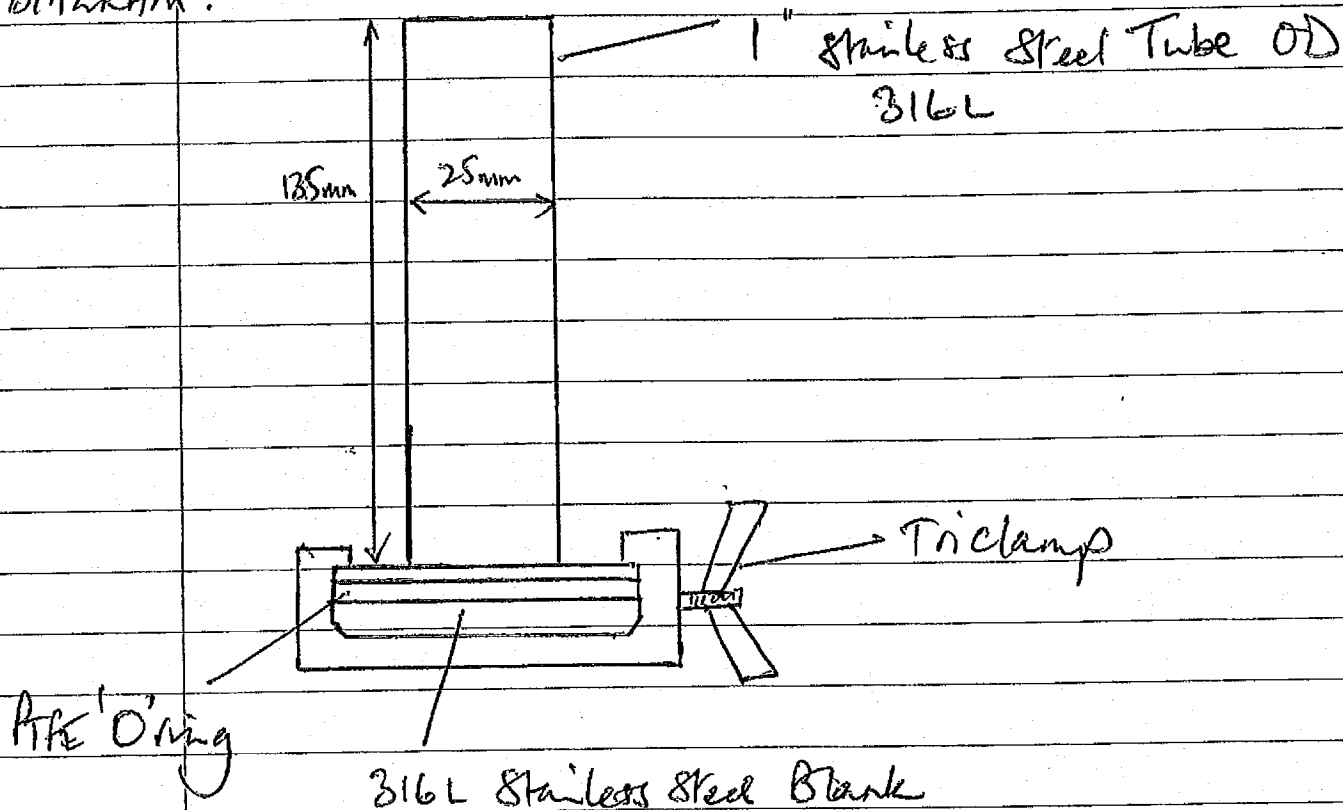
Time taken for homogenizing the
Silverson LR4

	START	END	TOTAL TIME.
Conc A	11.00	11.40	40 minutes
Conc. B	12.00	12.40	40 minutes
Conc. C	14.00	14.27	27 minutes
Conc. D	14.40	15.10	30 minutes

Aim:

Describe the type of vessel to be used in the heat sterilisation study for Brothamido Concentrate.

Diagram.



- NOTE:
- All stainless steel is 316L
 - All tubes have been passivated.
 - Manufactured by MJD Engineering.

AIM: To autoclave the Budesonide Concentrates at various temperatures and times in stainless steel vessels as described on LB137 P10.

SAMPLES:	Budesonide Concentrates	Budesonide	Polyborate 280
	Conc. A	37.5mg/ml	0.75mg/ml
	Conc. B	75 mg/ml	1.5mg/ml
	Conc. C	75 mg/ml	30mg/ml
	Conc. D.	150mg/ml	60mg/ml

EQUIPMENT: LTE Vacuum Autoclave S/N: J3063 (located in the microbiology lab at Goddard Road).

8x Stainless steel vessels

SAMPLES	AUTOClave HOLDING Temp	AUTOClave HOLDING TIME
A1 / A2	Control	Control
A3 / A4	110°C	120 mins
A5 / A6	121°C	20 mins
A7 / A8	121°C	30 mins
B1 / B2	Control	Control
B3 / B4	110°C	120 mins
B5 / B6	121°C	20 mins
B7 / B8	121°C	30 mins
C1 / C2	Control	Control
C3 / C4	121°C	20 mins
D1 / D2	Control	Control
D3 / D4	121°C	20 mins

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PR

Cycle 7

121°C for 30 mins.

cle is
Final c
Drains-
Precool
Printin
Stop re
Start r
Load fa
Safe lc
Holdins
Purgins
Purge
Steril
CLE 6

or use
ballast air
None
Ballast air
- 1.0 min
- 119.0 °C
- 119.0 °C
- 119.0 °C
80.0 °C
2.0 min

Cycle 6

121°C for 20 mins

cle is
Final
Drains

or use

Cycle 5

110°C for 60 mins.
But cycled Thrice.

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CYCLES N^o 1

L6137 P13

SIGNATURE

Cycle completed 13:42:43
CYCLE PASS

12:31:15	66.2	108.0	2.110
12:30:40	68.0	108.4	2.190
12:29:40	71.4	109.0	2.125
12:28:40	75.8	109.4	2.060
12:27:40	81.2	110.0	2.150
12:26:40	88.2	110.6	2.060
12:25:40	96.8	111.2	2.175
12:24:40	106.4	111.8	2.180
12:23:40	112.0	111.8	1.515
12:22:40	112.2	111.8	1.545
12:21:40	111.2	111.8	1.475
12:20:40	111.6	111.8	1.495
12:19:40	112.0	111.8	1.520
12:18:40	111.6	111.8	1.575
12:17:40	111.4	111.8	1.485
12:16:40	112.0	111.8	1.510
12:15:40	112.2	111.8	1.545
12:14:40	111.2	111.8	1.470
12:13:40	111.6	111.8	1.495
12:12:40	112.0	111.8	1.525
12:11:40	111.6	111.8	1.600
12:10:40	111.2	111.8	1.475
12:09:40	111.6	111.8	1.490
12:08:40	112.0	111.8	1.510
12:07:40	112.2	111.8	1.555
12:06:40	111.2	111.8	1.475
12:05:40	111.8	111.8	1.495
12:04:40	112.2	111.8	1.530
12:03:40	111.2	111.8	1.520
12:02:40	111.4	111.8	1.480
12:01:40	112.0	111.8	1.510
12:00:40	112.2	111.8	1.550
11:59:40	111.2	111.8	1.470
11:58:40	111.8	111.8	1.500
11:57:40	112.2	111.8	1.525
11:56:40	111.2	111.8	1.540
11:55:40	111.6	111.8	1.485
11:54:40	112.0	111.8	1.520
11:53:40	111.2	111.8	1.540
11:52:40	111.6	111.8	1.485
11:51:40	112.0	111.8	1.520
11:50:40	111.4	111.8	1.555
11:49:40	111.4	111.8	1.480
11:48:40	112.2	111.8	1.515
11:47:40	111.4	111.6	1.570
11:46:40	111.6	111.8	1.485
11:45:40	112.2	111.6	1.525
11:44:40	111.2	111.6	1.475
11:43:40	111.8	111.6	1.500
11:42:40	112.0	111.6	1.560
11:41:40	111.4	111.6	1.475
11:40:40	112.2	111.6	1.520
11:39:40	111.2	111.6	1.495

CYCLES N^o 2

L608 K

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SIGNATURE

Cycle completed 16:34:20

CYCLE PASS

15:22:30	65.2	108.0	2.095
15:22:00	67.2	108.4	2.120
15:21:00	70.8	109.0	2.080
15:20:00	75.2	109.6	2.200
15:19:00	80.8	110.0	2.130
15:18:00	87.8	110.6	2.075
15:17:00	97.0	111.2	2.195
15:16:00	106.4	111.8	2.200
15:15:00	111.8	111.8	1.515
15:14:00	112.0	111.8	1.540
15:13:00	111.2	111.8	1.498
15:12:00	111.6	111.8	1.500
15:11:00	112.0	111.8	1.525
15:10:00	112.0	111.8	1.570
15:09:00	111.2	111.8	1.485
15:08:00	111.6	111.8	1.505
15:07:00	112.2	111.8	1.535
15:06:00	111.4	111.8	1.560
15:05:00	111.4	111.8	1.490
15:04:00	111.8	111.8	1.510
15:03:00	112.2	111.8	1.540
15:02:00	111.0	111.8	1.500
15:01:00	111.4	111.8	1.495
15:00:00	111.8	111.8	1.515
14:59:00	112.2	111.8	1.545
14:58:00	111.0	111.8	1.490
14:57:00	111.6	111.8	1.495
14:56:00	112.0	111.8	1.520
14:55:00	112.0	111.8	1.565
14:54:00	111.4	111.8	1.480
14:53:00	111.8	111.8	1.505
14:52:00	112.2	111.8	1.530
14:51:00	111.2	111.8	1.505
14:50:00	111.6	111.8	1.490
14:49:00	112.0	111.8	1.520
14:48:00	111.6	111.8	1.590
14:47:00	111.4	111.8	1.480
14:46:00	112.0	111.8	1.510
14:45:00	112.2	111.8	1.560
14:44:00	111.2	111.8	1.470
14:43:00	111.6	111.8	1.495
14:42:00	112.0	111.8	1.535
14:41:00	111.2	111.8	1.470
14:40:00	111.8	111.8	1.500
14:39:00	112.2	111.8	1.540
14:38:00	111.2	111.8	1.470
14:37:00	111.0	111.8	1.500
14:36:00	112.2	111.8	1.540
14:35:00	111.2	111.8	1.470
14:34:00	111.8	111.8	1.500
14:33:00	112.2	111.8	1.545
14:32:00	111.2	111.8	1.475
14:31:00	111.8	111.8	1.505
14:30:00	112.0	111.8	1.575

CYCLE 5.

N^o 1 cycled first
then N^o 2 cycled
after.

N^o 1 + N^o 2 = 120 min

110°C for
60 mins +
60 mins.

NOTE These are
prints of a bottle
of water (1L) inside
the autoclave that
contains a temperature
probe. This probe
shows the temperature
of the inside of the
autoclave. Hence
this is equivalent to
the temperature of the
suspension in the
stainless steel vessels